UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,347	01/25/2002	Ronald M. Burch	200.1079CON2	8306

23280 7590 08/21/2007
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
08/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,347	BURCH ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/4/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed June 4, 2007 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 38 and 47-52 were pending. No claims were added, canceled or amended. Therefore, claim 38 and 47-52 are still pending and examined on the merits.

Withdrawn Objections/Rejections

4. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

5. Claims 38, 47, 48, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is **Feb 11, 1986**) in view of Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in clinical practice" *Seminars in Arthritis and Rheumatism*, **June 1997**, *26(1)*, 21-27).

For ***claim 38***, Baker et al. (see entire document) teach a method of effectively treating pain in humans comprising orally administering to a human patient an oral

dosage form comprising two analgesic compounds and or pharmaceutically acceptable salts thereof (e.g., see abstract, "Pharmaceutical compositions of narcotic analgesics [i.e., compound #1] and ibuprofen [i.e., compound #2] have been found to exhibit unexpectedly enhanced analgesic activity [i.e., pain relief] ... This synergism enables the use of lower doses of either or both drugs [i.e., two analgesic compounds] with a concomitant reduction in risk of possible side effects"; see also column 3, paragraph 1 wherein administration to a "human" is disclosed; see also column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone ... are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also Examples, especially Example 1 wherein use pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth; see also columns 3-8 wherein "single dosage form" is disclosed; see also columns 8 and 9 wherein sequential administration is disclosed; see also columns 3 and 4 showing "sustained release" formulations). In addition, Baker et al. disclose the use of oxycodone and or at least one pharmaceutically acceptable salt in the composition (e.g., see column 2, lines 44-48 wherein an "oral" dosage is disclosed, "Oxycodone ... are preferred because of their strong potency in oral dosage forms. Oxycodone is most preferred"; see also columns 1, 2, 8-10; see also Examples, especially Example 1 wherein use pharmaceutical dosage forms containing "only" oxycodone and ibuprofen are set forth).

For ***claim 47***, Baker et al. disclose a ratio of oxycodone and/or at least one pharmaceutically acceptable salt thereof to NSAID and/or at least one pharmaceutically acceptable salt thereof is from about 0 0001:1 to about 1:1 (e.g., see column 2, lines 14-

19, "(a) a narcotic analgesic [i.e., oxycodone], or a pharmaceutically acceptable salt thereof, and (b) ibuprofen [i.e., substituted by Meloxicam, see below], or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:1 to about 1:800. Preferred ratios of (a):(b) are from about 1:3 to about 1:400, and most preferred ratios are from about 1:30 to about 1:400"; see also claim 1).

For ***claim 48***, Baker et al. teach oxycodone is present in the pharmaceutically acceptable salt form (e.g., see claim 1, "A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or pharmaceutically acceptable salt thereof").

For ***claim 51***, Baker et al. disclose the use of NSAID from about 0 5 mg to about 1500 mg (e.g., see Example 1 wherein 60 mg of Ibuprofen NSAID is disclosed; see also Examples 2-24; see also columns 2 and 3).

For ***claim 52***, Baker et al. disclose oxycodone in an amount from 2.5 mg to 800 mg (e.g., see Example 1 wherein 5 mg is disclosed; see also rest of Examples 2-24; see also column 2; see also column 3, dosage forms section).

The prior art teachings of Baker et al. differ from the claimed invention as follows:

For ***claim 38, 47, 48, 51 and 52***, Baker et al. fail to disclose compositions with Meloxicam. Baker et al. only teach the use of NSAIDs like ibuprofen (e.g., see Baker et al., abstract)

However, Furst teach the following limitations that are deficient in Baker et al.:

For ***claim 38, 47, 48, 51 and 52***, Furst (see entire document) teach the use of

Meloxicam to alleviate pain in human patients (e.g., see figure 1; see also page 23, column 2, paragraph 1 "Nabumetone was significantly ... more effective than placebo and had comparable efficacy to naproxen or aspirin in the physicians' and patients' assessment of degree of pain ... [further studies] showed meloxicam [7.5 mg] to have efficacy approximately equal to that of nabumetone 1,000 mg"). Thus, Meloxicam is even more effective than other NSAIDs like Nabumetone at reducing pain and can be used in smaller dosages (i.e., 7.5 mg compare to 1,000 mg). Furthermore, Meloxicam exhibits less serious gastric and renal side effects than ibuprofen because it selectively inhibits COX-2 rather than COX-1 (e.g., see abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may ... [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2 selectivity than ... ibuprofen ... [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance ... With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) ... diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see

also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"; see also table 1 showing meloxicam has a better COX-2/COX-1 profiile than ibuprofen).

For ***claim 51***, Furst also disclose, for example, 7.5 and 15 mg doses (e.g., see Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substituted Meloxicam as taught by Furst for the ibuprofen in the ibuprofen/oxycodone compositions as taught by Baker et al. because Furst et al. shows that meloxicam is more potent than any other NSAID at reducing pain in clinical trials (e.g., see figure 2). Furthermore, a person of skill in the art would have been motivated to use Meloxicam not only because it is more potent but also because it is safer than other NSAIDs including the ibuprofen disclosed by Baker et al. (e.g., see see abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may ... [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2 selectivity than ... ibuprofen ... [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting

on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance ... With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) ... diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2"). Finally, a person of skill in the art would reasonably have expected to be successful because Meloxicam has been shown through extensive human clinical trials to be safe and effective especially with regard to the gastrointestinal tract (see Furst citations above), which is a preferred route of administration disclosed by Baker et al. (e.g., see Baker et al., column 4, line 13). In addition, Baker et al. explicitly state in the Background section that NSAIDs have been used to treat pain (e.g., see Baker et al., column 1, paragraph 3, "This patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic

analgesic is greater than for either alone which analgesic effect"), which would include Meloxicam (e.g., see abstract, "Nonsteroidal antiinflammatory drugs (NSAIDs) exert their actions by inhibiting cyclooxygenase (COX) ... A relatively selective COX-2 inhibitor ... [is] meloxicam [i.e., Meloxicam is an NSAID]"). Furthermore, Furst explicitly state that it is safer than ibuprofen (e.g., see Furst, page 22, column 1, last paragraph) that was disclosed by Baker et al. (e.g., see abstract).

Alternatively, it is submitted that the mere substitution of one component for another to yield predictable results represents a *prima facie* case of obviousness. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *12 (2007). Here, it would be obvious to make a simple substitution of Meloxicam for ibuprofen because it was known at the time of filing that the both provided the same antiinflammatory relief via inhibition of COX receptors (e.g., see Furst, abstract; see also Table 1). Furthermore, this substitution would have led to predictable results based on the combined teachings noted above because again it was well known that both drugs inhibit the same COX 1/2 receptors to produce the same/similar results. Thus, a person of ordinary skill in the art would have expected antiinflammatory efficacy whether ibuprofen or meloxicam was used.

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Baker reference does not teach or suggest the use of any NSAID, but solely teaches the use of a single specific NSAID, i.e., ibuprofen" (e.g., see 6/4/07 Response, page 5, paragraph 1).

[1] The Examiner respectfully disagrees. Baker et al. state, "This patent [referring to Sunshine] discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone" (e.g., see column 1, lines 22-25). It does not state, contrary to Applicants' assertions, that the analgesic effect is only greater for ibuprofen.

[2] Applicants argue, "The Baker reference included the Sunshine reference in the background section indicating that the invention of Baker was departing from (and not including) the disclosure of the sunshine reference ... [thus] the Sunshine reference teaches away from all but a select group of NSAIDs ... [which do] not include[e] meloxicam" (e.g., see 6/4/07 Response, page 5, paragraph 1).

[2] The obviousness rejection set forth above is based on the combination of the Baker and Furst, not a combination of Baker and Sunshine. The Sunshine reference only offers examples of prior art. Thus, Applicants' arguments are moot. The Baker reference clearly teaches the motivation to combine a narcotic analgesic and a NSAID drug. For example, Baker et al. state, "the analgesic effect of the combination of a selected NSAID and a selected narcotic

analgesic is greater than for either alone" (e.g., see column 1, lines 23-25). This provides ample motivation for a person of ordinary skill in the art to combine a selected NSAID and a selected narcotic analgesic drug to achieve a greater effect.

Furthermore, even if, *assuming arguendo*, the Sunshine reference was being combined in the manner suggested by Applicants (which is not the case, see above) the result would not change. For example, Furst states, "Double-blind, randomized trials in osteoarthritis and rheumatoid arthritis patients have shown equivalent anti-inflammatory efficacy among meloxicam 7.5 mg or 15 mg and diclofenac 100 mg ... [however] a double-blind, randomized, 28-day trial in over 9,000 patients showed that meloxicam 7.5 mg caused statistically less total GI toxicity, dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than diclofenac" (e.g., see Furst, abstract). Thus, Furst clearly teaches that meloxicam would be a good substitute for diclofenac disclosed in the Sunshine reference (e.g., see Sunshine, column 9, line 3). Likewise, Furst teaches that Meloxicam is better than many of the other NSAIDs listed in the Sunshine patent including piroxicam (e.g., see Furst, abstract, "meloxicam ... caused less endoscopically detected gastrointestinal (GI) damage ... than piroxicam"; see also Sunshine, column 11, line 26; see also columns, 16 and 17 wherein piroxicam is disclosed), naproxen (e.g., see Furst, abstract, "meloxicam caused less GI toxicity and fewer peptic ulcers and GI bleeds than naproxen, diclofenac, or piroxicam"; see also Sunshine, column 8, line 4 wherein naproxen is disclosed), ibuprofen (e.g., see Furst, page 22, column 1, last paragraph wherein a greater beneficial COX-2 selectivity is observed for Meloxicam relative to ibuprofen; see also Sunshine, column 17, line 8 wherein ibuprofen is disclosed), etc. Consequently, a person of ordinary skill in the art would understand after reading the Sunshine reference that meloxicam was a good substitute for a wide

range of structurally unrelated NSAIDs including the ibuprofen disclosed by Baker.

Finally, it should be noted that the Sunshine reference recites "the compositions and methods of the present invention can be selected from the following categories..." (emphasis added). Clearly, the recitation does not exclude other NSAIDs as erroneously purported.

[3] Applicants argue, "the chemical structure of the presently claimed NSAID, i.e., meloxicam: does not fall within any of the five structural categories indicated [in the Sunshine reference] above. Therefore, even assuming arguendo that the Baker reference contemplates the use of other NSAIDs based on the reference to the Sunshine reference, Applicants submit that the 'other' NSAIDs would be limited to the five structural categories listed in the Sunshine reference and would not include meloxicam" (e.g., see 6/4/07 Response, pages 5 and 6, especially page 6, middle paragraph).

[3] It is respectfully submitted that Applicants' arguments fail to appreciate the teachings of Furst, which explicitly state that meloxicam can be "substituted" for naproxen, diclofenac, piroxicam, ibuprofen, etc. as set forth in [2] above. Thus, the combined references teach meloxicam.

[4] Applicants argue, "the Sunshine reference is directed to combinations of caffeine and select NSAIDs ... [whereas] the present claims exclude the presence of caffeine by virtue of the 'consisting of' terminology" (e.g., see 6/4/07 Response, page 6, last paragraph).

[4] As noted above, the Sunshine reference is not being relied upon in the present rejection and, as a result, Applicants' arguments are moot. Sunshine merely provide some prior

art examples of NSAIDs as discussed in the background section of Baker. The Baker reference clearly teaches the motivation to combine a narcotic analgesic and a NSAID drug. For example, Baker et al. state, "the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone" (e.g., see column 1, lines 23-25). Thus, the fact that Sunshine may have used caffeine in some of its preferred embodiments is irrelevant. Furthermore, Furst explicitly states that Meloxicam has a more favorable COX-2/COX-1 selectivity (e.g., see Furst, page 22, paragraph bridging columns 1 and 2; see also Table 1).

[5] Applicants argue, "one of ordinary skill in the art would be motivated against replacing meloxicam for ibuprofen in the Baker reference, as none of the comparison studies for effectiveness of pain relieve discussed in the Furst reference include ibuprofen ... Thus ... one of skill in the art would not be motivated to substitute meloxicam for ibuprofen, as the reference does not provide one of ordinary skill in the art any indication as to the efficaciousness of meloxicam versus ibuprofen" (e.g., see 6/4/07 Response, page 7, paragraph 1).

[5] The Examiner respectfully disagrees. Furst teaches that selective COX-2 inhibitors will produce less troublesome and side effects such as the gastric and renal problems associated with the inhibition of COX-1 (e.g., see abstract). Thus, a compound that selectively inhibits COX-2 will, according to Furst, provide for a safer drug. Furst, further shows via a "comparison" study that Meloxicam exhibits a more favorable COX-2/COX-1 ratio than ibuprofen using human recombinant enzyme microsomal, the Human recombinant enzyme Transfected cos-cells, and the Human whole blood assays (e.g., see Furst, Table 1). Thus, contrary to Applicants' assertions, Furst has made a direct comparison between ibuprofen and

Meloxicam.

[6] Applicants argue, "There is conflicting evidence on the COX receptors and side effects associated with meloxicam and ibuprofen ... For example, Van Hecken et al. state that 'diclofenac, ibuprofen, and naproxen ... have shown in vitro to be inhibitors of both COX-1 and COX-2' and further describes side effects of meloxicam that result from COX-1 activity" (e.g., see 6/4/07 Response, paragraph bridging pages 7 and 8).

[6] First, the Examiner notes that Van Hecken et al. was published in 2000, three years after Applicants' earliest priority date and thus cannot represent the state of the art at the time of filing. Thus, Applicants' arguments are moot. Furthermore, even if, *assuming arguendo*, Van Hecken et al. could be relied upon to show the state of the art back in 1997 (which is not the case, see above) it is respectfully submitted that the reference is not inconsistent with the findings of Furst. Furst does not stand for the proposition that ibuprofen inhibits only COX-1 while Meloxicam inhibits only COX-2. Rather, Furst merely states that Meloxicam inhibits COX-2 to a greater extent that COX-1 and that it has a better COX-2/COX-1 profile than ibuprofen (e.g., see Table 1). Thus, less serious side effects would be expected for Meloxicam as compared to ibuprofen just as less serious side effects were noted for the other NSAIDs with less favorable COX-2/COX-1 profiles like diclofenac, piroxicam, etc.

[7] Applicants argue, "Even if there was agreement within the scientific community that meloxicam selectively inhibits COX-2, the reports of side effects of meloxicam have been conflicting and inconclusive. See, e.g., Rich et al. Ann Rheum Dis (2004) ... which provides a rank order of NSAIDs according to risk for GI complication, showing that meloxicam had a

higher risk of GI complications that ibuprofen and concluded that 'ibuprofen was the safest drug.'

[7] Again, it is noted that the article was published after the earliest effective filing date. Consequently, Applicants' arguments are moot. That is, a person of ordinary skill in the art at the time the invention was made (1997) would not have been deterred from a paper that was published seven years later (2004). Furthermore, even if, *assuming arguendo*, this publication could somehow be relied upon in the manner suggested by Applicants, Rich et al. merely set forth a few broad assertions about a select group of publications using statistical analysis, which not disprove the findings of Furst. For example, Rich et al. state, "the underlying disease requiring NSAID treatment may have a role in the development of GI damage. More studies are needed to assess this point clearly" (e.g., see page 764, column 2, third full paragraph). Thus, Rich et al. admit that they cannot determine "clearly" if the patients suffering from "osteoarthritis and rheumatoid arthritis" as set forth by Furst (e.g., see abstract) would have benefited more from Meloxicam or Ibuprofen because their studies were deficient in this regard. Furthermore, Furst used more than over 9,000 patients in one study and 5,600 patients in another, which speaks to its reliability.

[8] Applicants argue, "Additionally, Lanes et al. refer to previous studies in which 'there is no convincing evidence that the risk of the severest adverse gastrointestingal events ... is lower with meloxicam than with othe NSAIDs' ... [consequently] it is improper to assume that meloxicam would necessarily exhibit less serious gastric and renal side effects that ibuprofen" (e.g., see 6/4/07 Response, page 8, paragraph 1).

[8] Again, the Lanes et al. reference is published after the earliest effective filing date and thus cannot be used to ascertain the state of the art in 1997. Thus, Applicants' arguments are moot. Furthermore, even if, assuming arguendo, the Lanes et al. reference could be relied upon as suggested by Applicants it would not change the result. Lanes et al. only speaks to the "severest" adverse gastrointestinal event, not "all" adverse gastrointestinal events and thus does not disprove the broad teachings of Furst.

[9] Applicants argue, "There is no motivation to substitute the ibuprofen in the synergistic combination of the Baker composition with any other NSAID" (e.g., see 6/4/07 Response, page 8, last paragraph).

[9] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a person of skill in the art would have been motivated to use Meloxicam not only because it is more potent but also because it is safer than other NSAIDs including the ibuprofen disclosed by Baker et al. (e.g., see see abstract, "inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective COX-2 inhibitor, such as meloxicam, may ... [exhibit] improved tolerability"; see also page 22, column 1, last paragraph, "Meloxicam exhibited greater COX-2

selectivity than ... ibuprofen ... [which] preferentially inhibited COX-1"; see also "Safety of Meloxicam" section starting on page 24, especially, column 2, paragraph 1, "Meloxicam 7.5 mg caused no significant change in the mucosal appearance ... With piroxicam, there was a significantly higher number of endoscopically detected ulcers developing during the study compared with the meloxicam 15 mg group"; see also figure 2; see also page 24, column 2, paragraph 2, "During this large 4-week trial, GI side effects were significantly more common in the diclofenac group (19%) than in the meloxicam group (13%) ... diclofenac caused significantly more dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than meloxicam"; see also Table 2 showing meloxicam to be the "safest" NSAID especially with regard to gastrointestinal events; see also page 26, column 1, paragraph 1 showing meloxicam to be "well suited for the elderly" because the drug is "almost entirely converted to inactive metabolites before excretion"; see also Figure 3; see also Conclusions section, especially page 26, column 2, last paragraph, "Taken together, these results show that meloxicam has a good safety and efficacy profile, with some indication of increased GI safety over several other NSAIDs. The possible explanation for this profiles meloxicam's relatively selective inhibition of COX-2").

In addition, the Supreme Court has reversed this misuse of "rigid preventive rules" in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *7 (2007) ("the Court of Appeals ... conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try" ... Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our [Supreme Court] case law nor consistent with it"). Here, it would be obvious to make a simple substitution

of Meloxicam for ibuprofen because it was known at the time of filing that the both provided the same Cox-1/2 inhibition (e.g., see Furst, table 1) for the purposes of providing pain the same antiinflammatory relief (e.g., see Furst, abstract). Furthermore, the results would have been predictable based on the combined teachings noted above because they all inhibit the same COX receptors and the all produce the same results (albeit with different, yet predictable changes in the side effects).

[10] Applicants argue, "Baker reference teaches away from substituting ibuprofen with another NSAID (e.g., meloxicam), because of the unexpected synergy that it purports from the combination of ibuprofen with a narcotic analgesic" (e.g., see 6/4/07 Response, paragraph bridging pages 8 and 9).

[10] The Examiner respectfully disagrees. "[A] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend upon the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 478, 484 (1966)). However, a reference that "teaches away" does not *per se* preclude a *prima facie* case of obviousness, but rather the "teaching away" of the reference is a factor to be considered in determining unobviousness. Id 27 F.3d at 552, 31 USPQ 2d at 1132. Furthermore, the reference must deliberately seek to avoid the

proposed change. For example, in *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)) a system for measuring minute quantities of nitrogen presumably for the detection of drugs and explosives was examined. The claims were rejected as being obvious over Eads in view Warnick. Eads disclosed a method for separating and identifying sulfur compounds. Warnick disclosed a process for detecting pollutants in the atmosphere by measuring the level of nitric oxide. The PTO held that it would have been *prima facie* obvious to substitute the nitric oxide detector of Warnick for the sulfur dioxide detector of Eads. On appeal, the Federal Circuit reversed noting that Eads deliberately sought to avoid the use of nitrogen because the sulfur detector was adversely affected by substantial quantities of nitrogen. Thus, according to the CAFC, "instead of suggesting that the system be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention." See *Id.* at 1599. Thus, *Fine* provides an example of a "teaching away" by disclosing that the presence of a claimed element, nitrogen, is undesirable. No such "teaching away" exists in the present case. That is, Baker never states that Meloxicam won't work or that it will be undesirable to use it. Therefore, Applicants' arguments are moot.

[11] Applicants argue, "substituting meloxicam for ibuprofen would result in a dosage form which is not directed to the principle of operation described in the Baker reference" (e.g., see 6/4/07 Response, page 8, paragraph 2).

[11] To the extent that this argument is understood, it is submitted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly

suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Thus, a person of skill in the art would not need to use the same dosages for Meloxicam as were used for ibuprofen. A person of ordinary skill in the art would know enough to use the dosages that were taught, for example, in the Furst reference because these are the effective dosages for that drug.

[12] Applicants argue, "The Examiner is relying on an improper 'obvious to try' rationale" (e.g., see 6/4/07 Response, page 9, last paragraph).

[12] The Examiner respectfully disagrees. The Supreme Court has recently put a stop to this kind of "rigid preventive rules" in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *7 (2007) ("the Court of Appeals ... conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try" ... Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our [Supreme Court] case law nor consistent with it").

[13] Applicants argue, "In re O'Farrell is analogous to the present situation, where one of ordinary skill in the art would have to try each of numerous possible NSAIDs in place of ibuprofen in order to arrive at the selection of meloxicam" (e.g., see 6/4/07 Response, page 9, last paragraph).

[13] An invention is "obvious to try" where the prior art provides either no indication of which parameters would be critical or no direction as to which of many possible choices is likely

to be successful. *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807, 10 USPQ2d 1843, 1845 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989) (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)), which is clearly not the case here. Furst, for example, explicitly states that the COX-2/COX-1 selectivity is critical and further states that out of all the NSAIDs that could be chosen, meloxicam is the best. Thus, the critical factors have been well delineated by the prior art and the possible choices have been narrowed to just one.

[14] Applicants argue, "The Examiner is improperly picking and choosing meloxicam and oxycodone from the prior art ... it appears that the inventors in the Baker reference rejected all NSAIDs in their invention except ibuprofen" and cite various passages in the Baker reference to show that it mostly focused on ibuprofen (e.g., see 6/4/07 Response, pages 10-14).

[14] There's no evidence to suggest that Baker et al. knew anything about the benefits of meloxicam. Therefore, it cannot be proven, as was erroneously reported by Applicants, that Baker et al. "rejected all NSAIDS in their invention except ibuprofen." Furthermore, to the extent that applicants have impliedly argued that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

7. Claims 38 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. (U.S. Patent No. 4,569,937) (Date of Patent is Feb 11, 1986) in view of Furst (Furst, D. E. "Meloxicam: Selective COX-2 inhibition in clinical practice" Seminars in Arthritis and Rheumatism, June **1997**, 26(1), 21-27) and in further view of Oshlack I et al. US Pat. No. 5,472,712 (12/95) and/or Oshlack II et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier) and Iyengar et al. (WO 97/25988) (Date of Patent is **July 24, 1997**).

For ***claims 38, 47, 48, 51 and 52***, Furst and Baker et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 38, 47, 48, 51 and 52.

The combined prior art references of Furst and Baker et al. differ from the claimed invention as follows:

For ***claim 49***, the combined references of Furst and Baker et al. fail to teach the use of "a sustained release carrier which provides a sustained release of the oxycodone and/or ... salt thereof."

For ***claim 50***, the combined references of Furst and Baker et al. fail to teach the use of a sustained release of the meloxicam and/or salt thereof.

However, the combined references of Oshlack I/II et al. and Iyengar et al. teach the following limitations that are deficient in Furst and Baker et al.:

For ***claim 49***, the combined references of Oshlack I/II et al. and Iyengar et al. (see entire documents) teach the use of sustained release dosage forms for opioid analgesics,

including oxycodone, which utilize sustained release carriers employing beads which are coated with the opioid drug or which include substrate layers which include the drugs is known in the art to effectuate delayed release of extended duration (e.g., see Oshlack I, abstract, "A stabilized solid controlled release formulation ..."; see also column 14, paragraph 2, "A wide variety of therapeutically active agents can be used in conjunction with the present invention ... [including] oxycodone"; see also column 13, line 34; see also claim 6; see also claim 50; see also claim 62; see also claim 86; see also claim 108; see also Oshlack II, abstract, see also claims; see also examples; see also column 6, line 48; see also claim 5).

For ***claim 50***, the combined references of Oshlack I/II et al. and Iyengar et al. also teach the use of sustained release for Meloxicam (e.g., see Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses ... Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious ... Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to utilize sustained release carriers for oxycodone including beads/layers as taught by the the combined references of Oshlack I/II et al. and Iyengar for use in the Baker compositions since Baker specifically teaches using "sustained

release formulations." Furthermore, a person of ordinary skill in the art would have been motivated to use these formulations to delay drug release for extended duration (e.g., see Oshclack II, abstract, ""provide effective blood levels of the opioid analgesic for at least about 24 hours"). In addition, a person of skill in the art would have been motivated to use oxycodone in a sustained release dosage because, according to Oschlack I, "The present invention provides many benefits over prior art coatings, including, but not limited to, avoidance of organic solvents which have inherent safety concerns (flammability, carcinogenicity, environmental concerns, safety in general), and extended stability which may result in extended shelf life and expiration dating" (e.g., see Oschlack I, column 5, paragraph 3). Furthermore, Oshclack II state, "provide effective blood levels of the opioid analgesic for at least about 24 hours" using controlled release (e.g., see abstract). Finally, a person of skill in the art would have reasonably expected to be successful because the combined references of Oshlack I/II et al. and Iyengar teach that these formulations can be used for opioid analgesics like Applicants' preferred oxycodone or NSAIDs like Applicants' preferred Meloxicam (e.g., see Oshlack I, claims 6, 50, 62, 86 and 108; see also Iyengar et al., paragraph bridging pages 46 and 47, "The present invention encompasses ... Meloxicam"; see also page 47, first full paragraph, "The advantages of any synergistic combination therapy are obvious ... Sustained release formulations are now more feasible due to the lower amounts of active ingredient necessary"; see also paragraph bridging pages 48 and 49, "The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in

the art").

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue as discussed above the Baker reference in view of Furst fails to teach the claimed invention and that Oshlack I, Oshlack II and Iyengar fail to cure these deficiencies (e.g., see 6/4/07 Response, page 15).

The Examiner respectfully submits that there are no deficiencies for the reasons set forth above and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this

final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
August 16, 2007

/Jon D. Epperson/
Primary Examiner, AU 1639